Radiology

Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT: A Statement from the Fleischner Society[1]

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This report is to complement the original Fleischner Society recommendations for incidentally detected solid nodules by proposing a set of recommendations specifically aimed at subsolid nodules. The development of a standardized approach to the interpretation and management of subsolid nodules remains critically important given that peripheral adenocarcinomas represent the most common type of lung cancer, with evidence of increasing frequency. Following an initial consideration of appropriate terminology to describe subsolid nodules and a brief review of the new classification system for peripheral lung adenocarcinomas sponsored by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS), six specific recommendations were made, three with regard to solitary subsolid nodules and three with regard to multiple subsolid nodules. Each recommendation is followed first by the rationales underlying the recommendation and then by specific pertinent remarks. Finally, issues for which future research is needed are discussed. The recommendations are the result of careful review of the literature now available regarding subsolid nodules. Given the complexity of these lesions, the current recommendations are more varied than the original Fleischner Society guidelines for solid nodules. It cannot be overemphasized that these guidelines must be interpreted in light of an individual's clinical history. Given the frequency with which subsolid nodules are encountered in daily clinical practice, and notwithstanding continuing controversy on many of these issues, it is anticipated that further refinements and modifications to these recommendations will be forthcoming as information continues to emerge from ongoing research.

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In 2005, recommendations for the management of small pulmonary nodules were published as a statement from the Fleischner Society (1). Presently, these stand as the most frequently cited recommendations for the management of small pulmonary nodules detected at computed tomography (CT) (2). Despite widespread acceptance, however, important limitations have been recognized—particularly the lack of detailed consideration of subsolid lung nodules, both solitary and multiple (3). Although a number of recommendations for the management of subsolid nodules have been recently proposed, development of a standardized approach to the interpretation and management of these lesions remains critically important (4–9). As will be discussed, the need for the development of a consensus regarding management of these lesions is especially important given continued controversy about an optimal management strategy (10,11). This is made more urgent now that peripheral adenocarcinomas represent the most common type of lung cancer, ranging from 30% to 35% of all primary lung tumors, and with evidence of increasing frequency (12).

This report is to complement the original Fleischner Society recommendations by providing recommendations for subsolid nodules. Because several articles have recently reviewed key data pertinent to such proposals, the present approach will be to discuss those data that pertain to specific recommendations, as appropriate (4,9). The development of recommendations for management of subsolid nodules necessarily involves consideration of diverse issues, many of which remain controversial. These include variations in the definition of this subset of lesions as well as descriptive terminology, differences in methods of measuring lesions and determining interval growth, alternatives to CT characterization, including fluorodeoxyglucose (FDG) positron emission tomography (PET), and methods for obtaining definitive histopathologic correlation, including various methods for performing lung biopsy and resection. In addition, the recent publication of the classification system for peripheral adenocarcinomas of the lung sponsored by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) must be considered (13). Other important recent developments necessitating brief mention include the introduction of a recently updated TNM staging system for lung cancer (14,15) and preliminary results from the National Lung Cancer Screening Trial (16).

Following an initial consideration of appropriate terminology to describe subsolid nodules and a brief review of the new IASLC/ATS/ERS classification of peripheral adenocarcinomas of the lung, six specific recommendations were proposed—three regarding solitary subsolid nodules and three regarding multiple subsolid nodules. Each will be followed first by the rationale underlying the recommendation and then by specific pertinent remarks as appropriate to that particular recommendation (Table). Finally, issues for which future research is needed will be discussed.

Advance in Knowledge

- On the basis of the available evidence from the literature, this work proposes a set of recommendations specifically aimed at the management of subsolid nodules detected at CT.

Terminology

Currently, a number of terms have been used to describe focal nodular areas of increased lung attenuation, including both well and poorly defined lesions, through which normal parenchymal structures, including airways and vessels, can be visualized (17,18). This appearance typically is referred to as "ground glass" and, when localized, is most often described as either a ground-glass opacity (GGO) or a ground-glass nodule (GGN). Although these terms are often used interchangeably, for the purposes of this report "pure GGN" is preferred as the more precise descriptor. In distinction to pure ground-glass lesions, those that include a combination of both ground-glass and solid components, the latter obscuring underlying lung architecture, will be referred to as "part-solid GGNs" whereas the term "subsolid" nodules will be used to emphasize that both pure GGNs and part-solid GGNs are best considered as a category separate from purely solid lesions from a management perspective.

IASLC/ATS/ERS Classification of Lung Adenocarcinoma

Numerous studies have documented close correlations between CT and pathologic findings in patients with lesions in the spectrum of adenocarcinomas of the lung (19–23). Additional studies have also documented that small persistent pure GGNs, particularly those smaller than 5 mm, often represent foci of atypical adenomatous hyperplasia (AAH) (24). Furthermore, extensive data have documented that the larger the solid component of a lesion, the worse the prognosis (22,25–31).

Recently, a new IASLC/ATS/ERS classification of lung adenocarcinoma has been proposed (13). Although a detailed review remains outside the scope

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Abbreviations:
AAH = atypical adenomatous hyperplasia
AIS = adenocarcinoma in situ
ATS = American Thoracic Society
ERS = European Respiratory Society
FDG = fluorodeoxyglucose
GGN = ground-glass nodule
GGO = ground-glass opacity
IASLC = International Association for the Study of Lung Cancer
MIA = minimally invasive adenocarcinoma

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Guarantors of integrity of entire study, D.P.N., J.D.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, D.P.N., A.A.B., H.M., C.M.S.P., J.M.G., J.D.C., C.J.H., J.H.A., W.D.T.; clinical studies, D.P.N., J.D.C., J.H.A.; statistical analysis, J.D.C.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT: A Statement from the Fleischner Society

Nodule Type	Management Recommendations	Additional Remarks
Solitary pure GGNs		
≤5 mm	No CT follow-up required	Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN
>5 mm	Initial follow-up CT at 3 months to confirm persistence then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Solitary part-solid nodules	Initial follow-up CT at 3 months to confirm persistence. If persistent and solid component <5 mm, then yearly surveillance CT for a minimum of 3 years. If persistent and solid component ≥5 mm, then biopsy or surgical resection	Consider PET/CT for part-solid nodules >10 mm
Multiple subsolid nodules		
Pure GGNs ≤5 mm	Obtain follow-up CT at 2 and 4 years	Consider alternate causes for multiple GGNs ≤5 mm
Pure GGNs >5 mm without a dominant lesion(s)	Initial follow-up CT at 3 months to confirm persistence and then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Dominant nodule(s) with part-solid or solid component	Initial follow-up CT at 3 months to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with >5 mm solid component	Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for lung cancer

Note.—These guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic calipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.

of the present article, this classification has direct implications for the development of management guidelines based on CT findings (13). Briefly, this new classification calls for the elimination of the terms "bronchioloalveolar carcinoma" and "mixed subtype adenocarcinoma." Instead, based largely on surgical resections, the new system divides adenocarcinomas into the following categories: *(a)* premalignant lesions, including AAH and adenocarcinoma in situ (AIS), both defined as small lesions measuring 3 cm or less that demonstrate purely lepidic growth, and *(b)* malignant lesions, which were further subdivided into minimally invasive adenocarcinoma (MIA), defined as predominantly lepidic lesions measuring 3 cm or less with invasive components measuring no more than 5 mm, and invasive adenocarcinomas, which are further classified with comprehensive histologic subtyping to categorize lesions as predominantly lepidic, acinar, papillary, or solid patterns, with the addition of a newer micropapillary subtype. Finally, invasive mucinous adenocarcinomas (formally mucinous bronchioalveolar carcinoma) as a group are considered distinct from nonmucinous subtypes and AAH is retained as a premalignant lesion (13). Patients with AIS or MIA who undergo complete resection should have 100% or near 100% 5-year disease-free survival, respectively (32). For the overtly invasive adenocarcinomas, three additional grades have now been proposed, again emphasizing comprehensive histologic subtyping. These three grades include poor prognosis for solid micropapillary lesions, invasive mucinous adenocarcinomas, and colloid adenocarcinomas; favorable prognosis for nonmucinous lepidic lesions; and intermediate prognosis for papillary and acinar predominant adenocarcinoma subtypes (33).

For the purposes of this report, the IASLC/ATS/ERS classification will be emphasized despite a lack of definitive CT correlation; however, the older CT classifications, in particular that described by Noguchi et al (34), remain historically pertinent.

Recommendations for Managing Subsolid Lung Nodules

Although it is intended that these recommendations conform to those recommended in the initial Fleischner Society recommendations for solid lung nodules, a key distinction is that, in this article, individuals with a history of smoking are not consistently differentiated from ex-smokers or those who have never smoked, in part owing to concerns regarding an increasing incidence of adenocarcinomas in younger and nonsmoking individuals (1). Although smokers have a greater likelihood of developing cancer and tend to have a worse prognosis, there are insufficient data to support the use of different management guidelines based solely on smoking history (35). Similar considerations pertain to other known risk factors, including a family history of lung cancer and exposure to potentially carcinogenic agents. Also as distinct from the original Fleischner Society recommendations, which primarily focused on solitary solid lung nodules, the present recommendations include consideration of multiple subsolid nodules. This reflects the frequency with which multiple subsolid lesions are identified in this era of widespread availability of multidetector CT scanners. As before,

it cannot be overemphasized that these recommendations must be interpreted in light of an individual's clinical history.

The following recommendations are the result of careful review of the literature now available with regard to subsolid nodules. Given the greater complexity of these lesions, the following recommendations are more varied than the original Fleischner Society recommendations, warranting specific additional remarks to accompany each specific recommendation. For each recommendation, a specific grade is assigned as per the American College of Chest Physician Task Force recommendations for grading strength of recommendations (36).

Recommendation 1

Solitary, pure GGNs measuring 5 mm or less do not require follow-up surveillance CT examinations (Table).

Grade 1C: Strong Recommendation, Low or Very Low Quality Evidence

Rationale.—Although many of these lesions likely represent incidental foci of adenomatous hyperplasia, there are reasons not to recommend routine use of long-term CT follow-up at this time. First, although an association between AAH and adenocarcinoma has been reported, it is unknown how often, if ever, incidentally identified isolated foci of AAH progress to invasive carcinomas. These lesions are typically stable or extremely indolent at follow-up over several years (5,37–39). Second, screening CT studies have shown that the doubling time of larger pure GGNs is on the order of 3–5 years on average, making the detection of a relevant increase in size problematic (40,41). Finally, the precision with which small lesions measuring 5 mm or less can be measured by using currently available measuring techniques is limited, rendering precise determination of interval growth susceptible to substantial inter- and intraobserver variability (42,43). The likely result is that routine follow-up CT examinations for such lesions would result in numerous inconclusive studies at the expense of considerable monetary cost and excess radiation exposure (44).

Figure 1

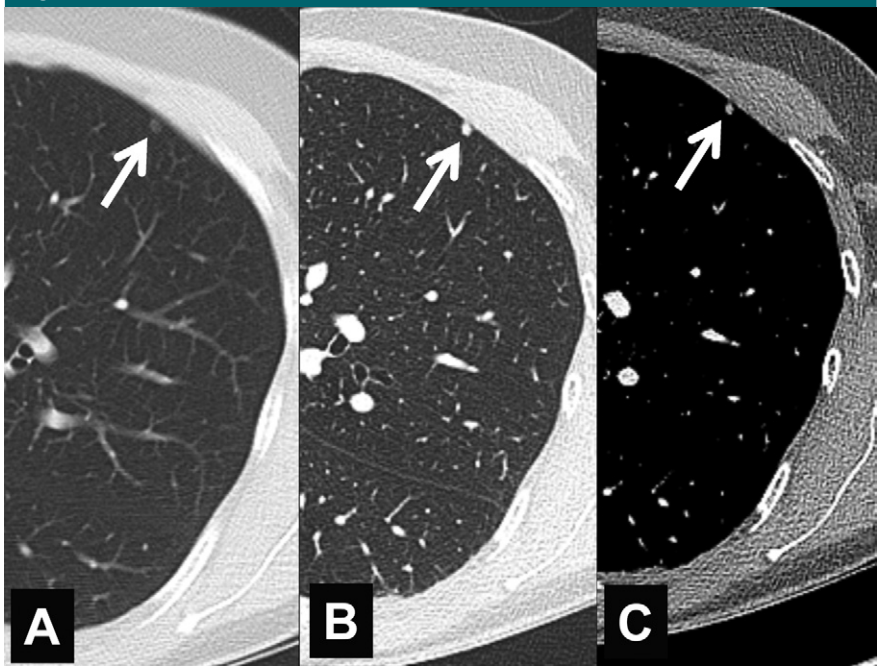

Figure 1: Use of thick versus thin sections for accurate characterization of a 5-mm subsolid nodule (arrow) in lung periphery. *A,* CT scan obtained with 5-mm-thick sections through left upper lobe shows a small apparently pure GGN in lung periphery. *B, C,* CT scans obtained with 1-mm-thick sections at same level reconstructed from original volume acquisition images with lung (*B*) and soft-tissue (*C*) windows show that nodule is actually a solid lesion, likely a calcified granuloma.

Additional remarks.—1.1. It is necessary to establish lesions as true GGNs, preferably by using contiguous thin CT sections (1 mm thick) whenever possible to avoid the pitfall of interpreting lesions as subsolid on thick sections (typically 5 mm) when they are actually solid (Fig 1) (45).

1.2. When evaluating pure GGNs, regardless of size, a history of extrathoracic malignancy does not necessarily preclude following these guidelines because data support the rarity with which pure GGOs prove to be metastatic in nature (46,47).

Recommendation 2

Solitary, pure GGNs larger than 5 mm require an initial follow-up CT examination in 3 months to determine persistence, followed by yearly surveillance CT examinations for a minimum of 3 years if persistent and unchanged (Table).

Grade 1B: Strong Recommendation, Moderate Quality Evidence

Rationale.—According to the recently proposed IASLC/ATS/ERS classification, these lesions correspond to preinvasive AAH or AIS sufficiently often to warrant a conservative approach emphasizing long-term CT surveillance (48). Key to this recommendation is the fact that there is no reliable method currently available short of surgical resection with which to characterize these lesions pathologically as premalignant, malignant, or benign. As a consequence, only a few reports have suggested that pure GGOs measuring at least 8 mm should be resected routinely (5). Persistent pure GGNs prove to be benign in up to 20% of cases (19,48,49), with considerable overlap in morphology between benign and malignant subsolid nodules (19,50). Because most of these lesions prove either to be benign or to represent isolated foci of AAH, AIS, or MIA, close monitoring is appropriate

Figure 2

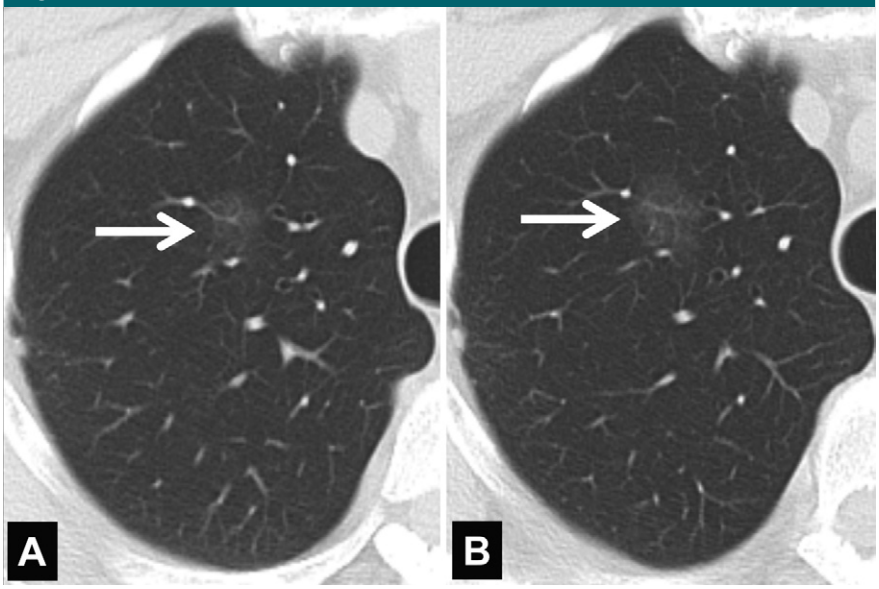

Figure 2: Value of contiguous 1-mm-thick CT scans for establishing subtle interval growth. *A,* Magnified section through right upper lobe shows a subtle pure GGN (arrow). *B,* Follow-up scan obtained 20 months later allows comparison at precisely the same anatomic level, which is easily confirmed by comparison of adjacent vessels. In this case, a subtle increase in lesion size (arrow) is definitively established. Follow-up resection documented stage IA lepidic invasive adenocarcinoma.

to enable early detection of even subtle interval change in their appearance, obviating unnecessary surgery and potentially avoiding overdiagnosis in cases in which no change is identified (9,48,51).

Close monitoring should also allow early identification of lesions that prove to be adenocarcinomas manifesting as pure GGNs (Fig 2) (52). Factors that predispose to interval growth include nodule size larger than 10 mm and a history of lung cancer (53). Most important, in at least one study of subsolid lesions that were resected only after evidence of interval growth at follow-up surveillance CT, the resulting delay in diagnosis had no adverse effect on patient outcomes (54).

It should be noted that the recommendation for initial 3-month follow-up CT of the entire thorax is based on the following considerations. First, both pure GGNs and part-solid nodules have been documented to disappear at short-term follow-up (55,56). Establishing resolution allows avoidance of otherwise prolonged patient uncertainty and anxiety (Fig 3). Initial short-term follow-up also ensures the identification of occasional rapidly enlarging lesions, as can occur, for example, in patients with mucinous adenocarcinoma (Fig 4). Second, performing short-term follow-up also enables acquisition of a baseline thin-section data set if not obtained initially. As will be discussed below, acquiring contiguous 1-mm-thick sections is an important consideration in optimizing detection of subtle indolent nodule growth, especially for pure GGNs.

Additional remarks.—2.1. Currently, there is no indication for an initial course of antibiotics (57).

2.2. Accurate surveillance requires consistency in CT technique. Although the initial CT examination may have been reconstructed with use of 5-mm-thick sections, follow-up examinations should include contiguous 1-mm-thick sections with use of a low-dose technique (58,59).

2.3. FDG PET/CT is unlikely to be of value because small pure GGNs are usually negative at PET. In addition, it is unlikely to provide additional information regarding nodal status or extrathoracic involvement in these characteristically localized lesions, especially those measuring less than 10 mm (60–67). As reported by Yap et al (68), of 46 subsolid lesions with surgically documented "mixed" adenocarcinomas, 67% of those with pure GGNs had negative findings at PET. Similar findings were also reported by Heyneman and Patz (62), who found that the overall sensitivity of PET for patients with pathologically proved bronchioloalveolar cell carcinoma was only 38%.

2.4. In cases in which conservative nonsurgical management is clinically indicated, percutaneous transthoracic needle biopsy is not routinely recommended for pure GGNs (69). First, the diagnostic yield of these lesions is poor and potentially misleading. In a study of the accuracy of CT-guided transbronchial needle biopsy for lesions smaller than 2 cm, Shimuzi et al (70) found the overall diagnostic yield to be 65%; however, the diagnostic yield was only 51% for GGO-dominant lesions (GGO ratio <50%) and only 35% for GGO-dominant lesions smaller than 10 mm. Similarly, in a recent study of 110 fine-needle aspiration biopsies performed in patients with suspicious lesions identified at low-dose screening examinations, unsatisfactory results were obtained in 24 (71). Although the diagnostic yield for subsolid nodules can be substantially higher with percutaneous transthoracic core needle biopsy (72), discordant diagnoses at transbronchial needle biopsy versus open lung biopsy remain problematic. Second, there is evidence that delay in surgical resection for slow-growing pure GGNs does not affect subsequent staging, especially for those patients in whom careful follow-up surveillance CT scans are obtained (54). As a consequence, transthoracic needle biopsy should be considered only for those cases in which a surgical option is not deemed clinically appropriate.

2.5. Although previous reports have suggested that pure GGNs larger than 10 mm should be resected when persistent, this decision should reflect

the clinical context in which these lesions appear. This would include, for example, the patient's age, given documented prolonged doubling times. For lesions that enlarge and/or increase in attenuation, consideration should be given to surgical resection, including video-assisted thoracic surgical wedge, segmental, or subsegmental resections. In this setting, transbronchial needle biopsy should only be considered for nonsurgical candidates for whom alternate methods of therapy are proposed (eg, stereotactic radiation therapy or thermal ablation).

2.6. Although a number of sophisticated approaches to nodule quantification have been proposed, including methods for detecting a change in size and/or attenuation, no consensus regarding an optimal approach has been sufficiently validated to be recommended. When electronic calipers are used, bidimensional measurements can be obtained to help optimize the detection of subtle changes, especially in poorly marginated lesions. Regardless of the approach used, however, it should be emphasized that the method chosen should be consistently applied to all subsequent examinations and that follow-up CT scans should always be compared with those from the earliest available study (see Recommendation 3, additional remark 3.3).

Figure 3

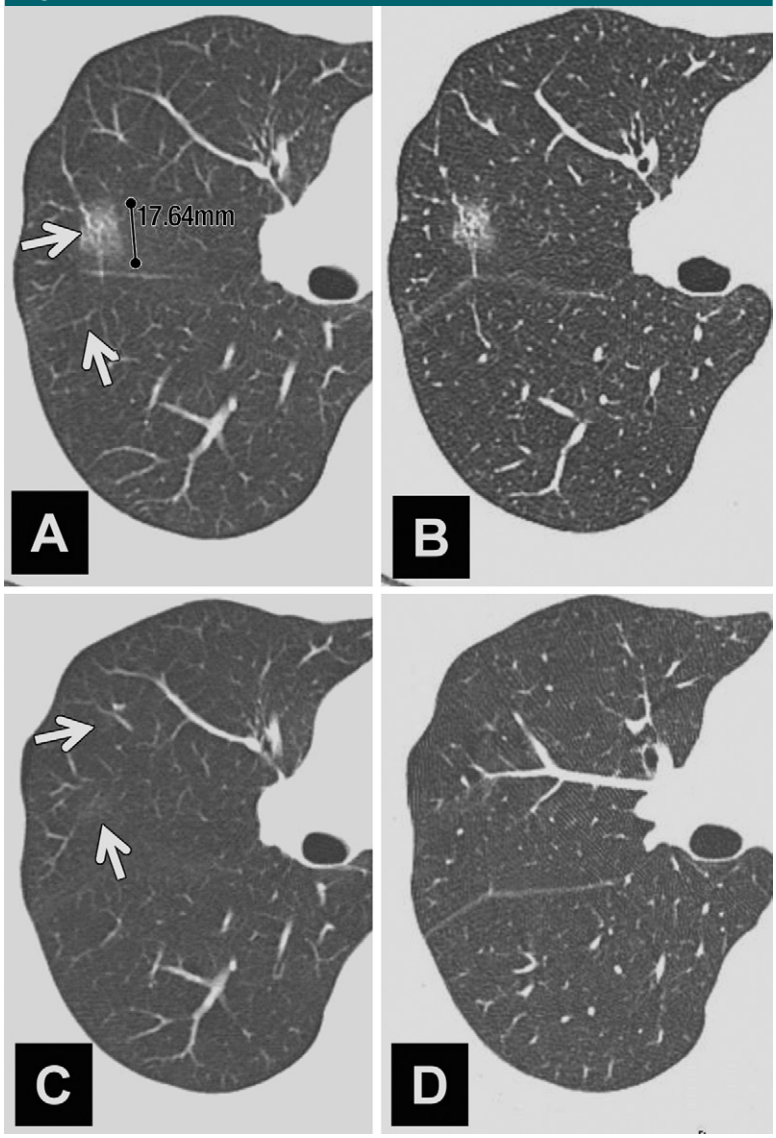

Figure 3: Value of initial short-term follow-up of benign GGNs. *A, B,* Target reconstructed 5-mm-thick (*A*) and 1-mm-thick (*B*) sections through right upper lobe show a focal ground-glass lesion (upper arrow in *A*), within which a few dilated peripheral airways can be identified. This appearance is strongly suggestive of a peripheral adenocarcinoma. Lower arrow in *A* points to normal lung. *C, D,* CT scans obtained with 5-mm-thick (*C*) and 1-mm-thick (*D*) sections 3 months later at same level as *A* and *B* show near-complete disappearance of lesion, likely representing focal nonspecific inflammation. Arrows in *C* indicate subtle new foci of ground-glass attenuation appearing in the interval, again consistent with nonspecific inflammation.

Recommendation 3

Solitary part-solid GGNs, especially those in which the solid component is larger than 5 mm, should be considered malignant until proved otherwise provided either growth or no change is seen at a follow-up CT examination performed in 3 months.

Grade 1B: Strong Recommendation, Moderate Quality Evidence

Rationale.—Unlike pure GGNs, numerous studies have documented that part-solid GGNs have a sufficiently greater likelihood of being malignant than pure GGNs and thus warrant an aggressive diagnostic approach (73). As reported by Henschke et al (74) in a study of 233 instances of positive findings at baseline low-dose CT screening examinations, among 44 (19%) resected subsolid lesions, malignancy was diagnosed in 15 (34%). The malignancy rate for solid nodules was 7% ($P < .001$). Importantly, the malignancy rate for part-solid GGNs was 63%, compared with 18% for pure GGNs (74). Even after adjusting for size, the malignancy rate for part-solid GGNs again proved significantly higher than that for either solid or pure GGNs ($P = .03$). Similar to solid lesions, large pure GGNs are more likely to be invasive (6,47,48,74,75).

Figure 4

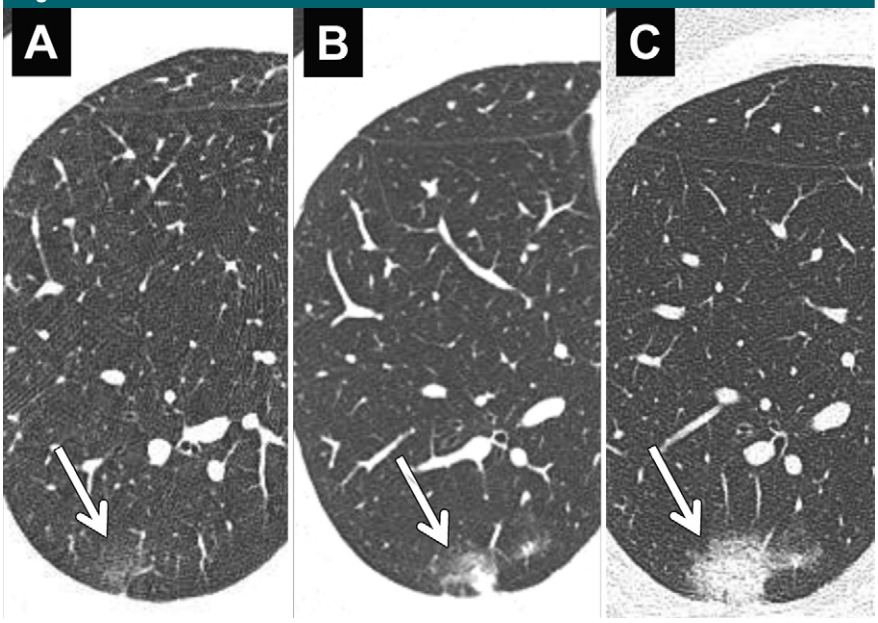

Figure 4: Value of initial short-term follow-up of malignant GGNs. Consecutive 1-mm-thick sections through right lower lobe section obtained at same anatomic level over a 6-month period (*A*, baseline; *B*, 3 months; *C*, 6 months) show rapid transformation of initial pure GGN (arrow in *A*) to a predominantly part-solid lesion (arrow in *B* and *C*), which subsequently proved to be mucinous adencarcinoma.

Although the development of a solid component within lesions is also strong evidence of an invasive adenocarcinoma (6,20,21,47,74,76), lesions in which the solid component measures 5 mm or less represent an important potential exception, as these lesions frequently prove to be either AIS or MIA, for which conservative management may be indicated. The overall dimensions of nonsolid nodules and their solid components, as described herein, are based on the average of long and short dimensions. The size of the solid component is best measured in its largest dimension visible on transverse CT sections, on thin sections with a mediastinal window setting.

Additional remarks.—3.1. Because these lesions may disappear at follow-up, it is strongly advised that at least one follow-up CT scan be obtained in 3 months to confirm persistence (77). Factors reported to be predictive of the transient nature of these lesions include younger age, female sex, higher risk of lung cancer, smoking history, multiplicity, eosinophilia, and, surprisingly in one report, a larger size of the solid component (77). Importantly, care should be taken not to assume that all lesions that decrease slightly in size are necessarily benign as it is well documented that adenocarcinomas can decrease temporarily in size owing to fibrosis or atelectasis (21,56,78). However, such change is often associated with a corresponding increase in attenuation.

3.2. Measurement of the size of the solid components and determination of the percentage of solid versus ground-glass components of subsolid lesions are important because it has been shown that the greater the extent of the solid component, the more likely the lesion will be an invasive adenocarcinoma with an associated poorer prognosis (31,79–83).

3.3. Although a number of proposals for the quantitative evaluation of subsolid nodules have been offered, at present there is no consensus regarding an optimal approach (29,30,42,49,76,78,84–93). Despite limitations of any given method, the specific technique chosen should be applied consistently from one examination to the next to minimize both intra- and interobserver variability. Similar to recommendations regarding pure ground-glass lesions, follow-up should be performed with contiguous low-dose, thin-section CT. When electronic calipers are used, the solid component should be evaluated with narrow and/or mediastinal windows and the ground-glass component should be measured with wide and/or lung windows, with measurements based on the average of long and short axial dimensions recommended (Table) (1).

3.4. Special consideration may be given to those cases in which the solid component is barely visible or is smaller than 5 mm (Fig 5). With use of the recent IASLC/ATS/ERS classification, these lesions, if neoplastic, are classified as MIAs. Although they have been shown to have a near 100% disease-free interval if completely resected, a more conservative approach similar to that proposed for pure GGNs may be considered in the appropriate clinical context (eg, in patients considered poor surgical candidates).

3.5. For part-solid GGNs measuring 8–10 mm, further evaluation with FDG PET/CT is advisable before more invasive procedures both for more accurately assessing prognosis as well as optimizing preoperative staging (61,94–100).

3.6. Similar to recommendations regarding the use of transbronchial needle biopsy for pure GGNs larger than 5 mm (additional remark 2.4), transbronchial needle biopsy is not recommended for part-solid nodules unless surgery is not considered a viable alternative. In cases for which surgical resection is considered appropriate, data strongly suggest that limited video-assisted thoracoscopic surgical wedge or segmental resections may be considered in place of a standard lobectomy (20,22,26,79,101–103).

Recommendation 4

Multiple well-defined GGNs all measuring 5 mm or less should be conservatively managed with follow-up CT examinations performed at 2 and 4 years (Table).

Grade 1C: Strong Recommendation, Low or Very Low Quality Evidence

Rationale.—Although the likelihood of any one of multiple GGNs smaller than 5 mm evolving into an invasive adenocarcinoma has not been determined (5,37–39), conservative management is recommended given the frequent finding of an additional focus of AAH in patients with surgically resected adenocarcinomas, with follow-up CT examinations performed at 2 and 4 years (5,37–39) (Fig 6).

Additional remark.—4.1. Consider alternate diagnoses for multiple extremely small ground-glass lesions, including, for example, respiratory bronchiolitis in smokers.

Recommendation 5

In cases in which multiple pure GGNs are identified, at least one of which is larger than 5 mm, and in the absence of a dominant lesion, an initial follow-up

Figure 5

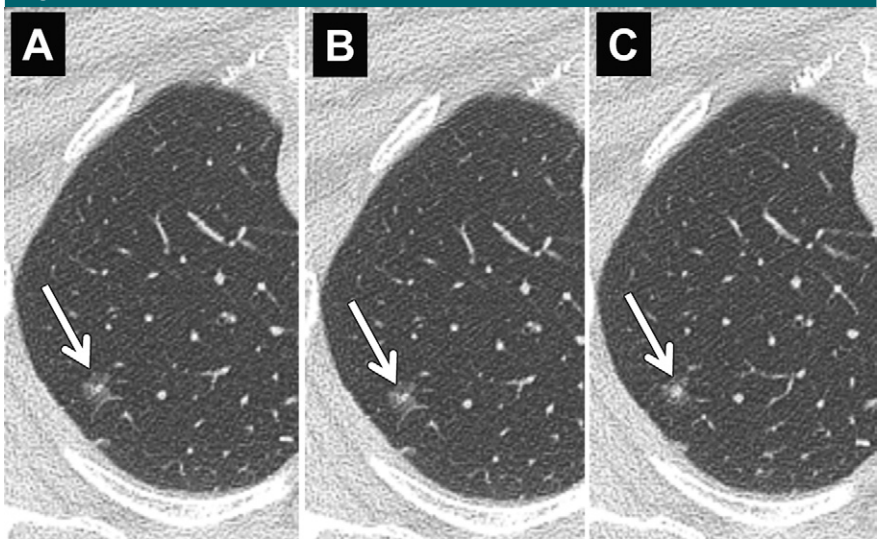

Figure 5: Part-solid nodules with solid component smaller than 5 mm. *A–C,* Contiguous 1-mm-thick sections through right upper lobe show a small peripheral lesion (arrows) in which a small solid component (<5 mm) can be identified. Contiguous 1-mm-thick sections allow confident identification of truly solid components distinct from crossing vessels. Because the appearance was consistent with that of possible MIA, this lesion was conservatively followed up without change in form over 2 years.

Figure 6

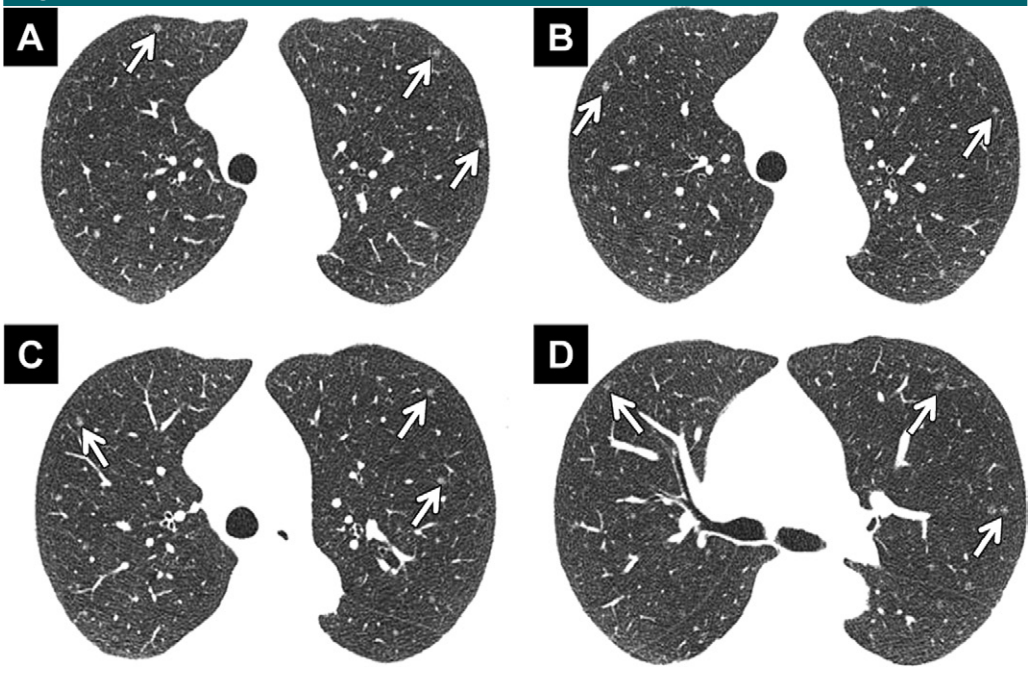

Figure 6: Multiple GGNs smaller than 5 mm. *A–D,* CT scans obtained with 1-mm-thick sections show numerous scattered GGNs (arrows), all of which were smaller than 5 mm. Although the likelihood of any one of these progressing to an invasive adenocarcinoma is likely no greater than that for a solitary lesion, conservative management is recommended, with follow-up CT examinations at 2 and 4 years.

Figure 7

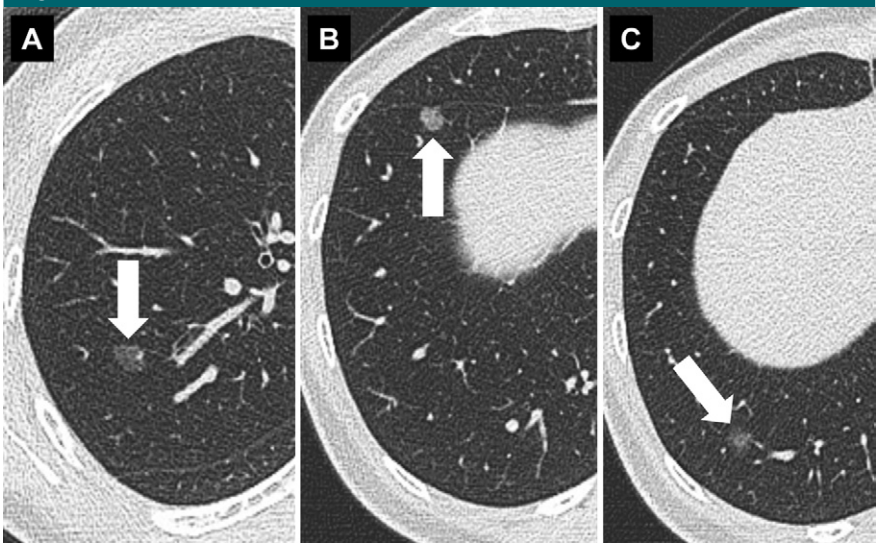

Figure 7: Multiple GGNs larger than 5 mm in the absence of a dominant lesion. CT scans obtained with 1-mm-thick sections through right upper lobe (*A*) and lower lobes (*B, C*) show three separate GGNs larger than 5 mm (arrows), all of approximately the same size. In the absence of a dominant lesion, conservative management with an initial follow-up examination in 3 months followed by yearly CT examinations was recommended.

CT examination in 3 months is recommended, followed by long-term yearly surveillance CT examinations for at least 3 years (Table).

Grade 1B: Strong Recommendation, Moderate Quality Evidence

Rationale.—The rationale behind this recommendation is essentially the same as the rationale proposed in Recommendation 2. Although available data are conflicting regarding the likelihood of malignancy in solitary versus multiple pure GGNs, with some studies suggesting that invasive carcinomas are more likely to arise in larger lesions (5), conservative management with long-term yearly CT surveillance is still recommended regardless of smoking history in those cases in which no clearly dominant lesion(s) is identified (see Recommendation 6 for further definition of a dominant lesion) (Fig 7).

Additional remark.—5.1. Similar remarks proposed for Recommendation 2 equally apply to cases in which there are multiple pure GGNs. These include use of consistent CT technique with follow-up low-dose contiguous thin-section CT (see additional remark 2.2); no indication for routine use of FDG PET/CT, especially for lesions measuring 8 mm or less to 10 mm (see additional remark 2.3); no indication for routine transbronchial needle biopsy (see additional remark 2.4); and consistent measurement technique for all follow-up examinations (see additional remark 2.6).

Recommendation 6

In cases with multiple subsolid nodules in which a dominant lesion(s) can be identified, the dominant lesion(s) determines further management. After an initial follow-up CT examination in 3 months that confirms persistence, an aggressive approach to diagnosis and management is recommended, especially for lesions with solid components larger than 5 mm (Table).

Grade 1C: Strong Recommendation, Low or Very Low Quality Evidence

Rationale.–Although at present there is no reliable method with which to differentiate multiple synchronous cancers from intrapulmonary metastases, reports in which genetic profiling and comprehensive histologic subtyping have been performed document that multiple subsolid lesions are typically synchronous primary cancers for which surgical resection(s) may be indicated, with the exception of patients with a history of mucinous adenocarcinoma (5,104). Although there is no currently agreed upon definition of a dominant lesion, part-solid GGNs, especially those with solid components larger than 5 mm, pure GGNs larger than 10 mm, atypical subsolid nodules with spiculated contours, "bubbly" appearance or reticulation, pure GGNs or part-solid nodules with solid components smaller than 5 mm that demonstrate interval change in size or attenuation, or solid lesions with characteristics suspicious of invasive carcinoma should be interpreted with a high degree of suspicion (Fig 8). Multiple primary lung carcinomas can be found in 8%–22% of surgically resected cases (105,106) and in up to 18% of patients with adenocarcinoma detected in CT screening programs (83). Most patients with lung cancer who present with multiple nodules, particularly multiple GGNs or part-solid lesions, actually have synchronous primary carcinomas. Accumulating surgical data favors aggressive treatment of these patients because their survival is comparable to that of patients with solitary lung cancers of comparable stage (83,107–109).

Additional remarks.—6.1. Similar to remarks applying to part-solid GGNs outlined above for Recommendation 3. In particular, consideration should be given to the use of FDG PET/CT (see additional remark 3.5) to further characterize lesions measuring 8–10 mm.

6.2. In patients with multiple lesions in whom surgery is indicated, limited video-assisted thoracoscopic surgical wedge or segmental resections should be considered given recent documentation of long-term survival following multiple sublobar resections (75,101–103).

6.3. In cases with lung cancer documented with surgical resection, continued yearly surveillance for at least 3 years is recommended, with the expectation that new malignant lesions may arise in a small percentage of cases (75).

Figure 8

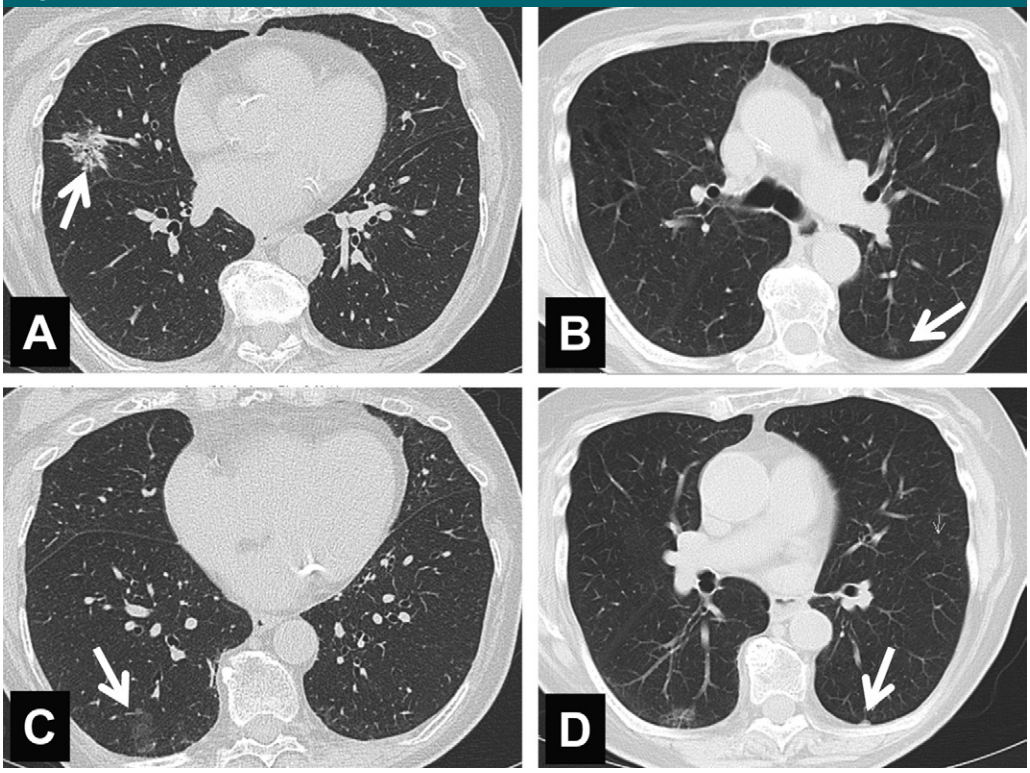

Figure 8: Multiple subsolid lesions with single dominant focus. *A–D,* CT scans obtained with 1-mm-thick sections at same time in same patient show a variety of lesions (arrows) in both lungs. Lesion in middle lobe (*A*) is clearly larger and more complex than the others. Stage IA invasive lepidic adenocarcinoma was diagnosed at histologic examination of specimen from follow-up wedge resection.

Future Considerations

Despite more than a decade's worth of reports, a number of ongoing issues regarding subsolid nodules remain to be determined.

1. How often, if ever, does AAH or AIS actually progress to invasive adenocarcinoma? In one study evaluating serial changes in 48 subsolid nodules identified at low-dose CT screening over a mean interval of 450 days (range, 85–951 days) that were subsequently proved to be either foci of AAH or Noguchi type A–C lesions, those initially identified as pure GGNs increased in size in 75% of cases and subsequently developed solid components in 17%, with further enlargement of solid components identified in 23% of cases (21). Obtaining more data regarding the actual evolution of these lesions remains an important objective for further research, including consideration of the likelihood of progression in solitary versus multiple lesions.

2. How do CT findings correlate with the new IASLC/ATS/ERS classification? Although it is likely that similar correlations as previously determined for CT–World Health Organization correlations will remain, this requires prospective validation.

3. What is the role of biomarkers in establishing the diagnosis of invasive carcinomas? Can biomarkers be used to determine phenotype and help differentiate indolent from more aggressive lesions (110)?

4. Is conservative lung-sparing surgery truly indicated in patients with subsolid nodules suspected of being invasive carcinomas? What are the optimal surgical techniques to be used in this setting?

5. Pending further prospective data regarding the natural history of subsolid nodules, there is a clear need for further research to develop reliable quantitative methods with which to longitudinally assess subsolid nodules. Although a number of interesting proposals have been published, to date there is insufficient corroboration to recommend any of these.

6. Presently, the implications of the initial results from the National Lung Cancer Screening Trial remain uncertain, whereas further data from that trial that may affect management strategies for subsolid nodules have yet to be analyzed.

7. What are the implications, if any, of measuring the size of the solid versus ground-glass components of part-solid nodules for future revisions of the TNM staging system for lung cancer (111)? Pathologic and CT data are emerging to suggest that measurement of the size of the invasive component of lesions (corresponding to the size of the solid component at CT) is more predictive of

survival than total tumor size in adenocarcinomas with a lepidic component (112). Data are needed that incorporate quantitative CT measurements to further test this hypothesis.

8. Finally, and perhaps most important, is there a danger of overdiagnosis of lung cancer? It is possible that many small cancers, especially those defined as AIS and even MIA, may never result in death. Although this clearly remains controversial, a comparison of cancers identified at baseline low-dose CT screening (prevalence cancers) and those identified at yearly follow-up studies (incidence cancers) found that baseline screening yielded a greater number of subsolid cancers, which were predominantly adenocarcinomas (113). The influence of ethnicity and sex on the likelihood of subsolid nodules representing tumors will also require greater study.

Given the frequency with which subsolid nodules are encountered in daily clinical practice, and notwithstanding continuing controversy on many of these issues, the need for a set of current recommendations is clearly evident. It is anticipated that further refinements and modifications to these recommendations will be forthcoming as information continues to emerge from ongoing research.

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